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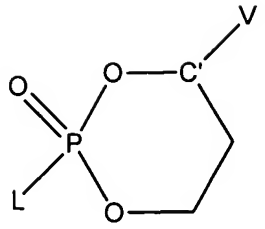
We Claim:

1. A compound of Formula I:



Formula I

wherein:

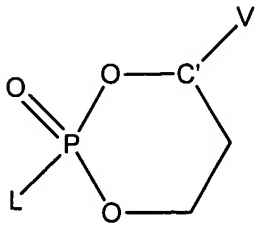
V and L are *trans* relative to one another;

V is selected from the group consisting of carbocyclic aryl, substituted carbocyclic aryl, heteroaryl, and substituted heteroaryl;

L is a leaving group selected from the group consisting of halogen, alkyl sulfonate, aryloxy optionally substituted with 1-2 substituents, N-containing heteroaryl, and N-hydroxy-nitrogen containing heteroaryl;

and salts thereof.

2. The compounds of claim 1:



Formula I

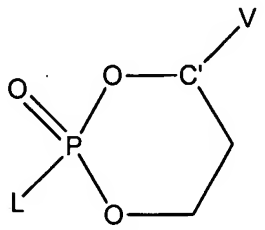
wherein:

V and L are *trans* relative to one another;

V is selected from the group consisting of phenyl, and monocyclic heteroaryl, all optionally substituted with 1-4 substituents; and

L is a leaving group selected from the group consisting of halogen, and aryloxy optionally substituted with 1-2 substituents.

3. The compounds of claim 2:



Formula I

wherein:

V and L are *trans* relative to one another;

V is selected from the group consisting of phenyl and N-containing heteroaryl, all optionally substituted with 1-4 substituents;

L is a leaving group selected from the group consisting of halogen, and aryloxy optionally substituted with 1-2 substituents.

4. The compounds of claim 3 wherein V is selected from the group consisting of phenyl optionally substituted with 1-4 substituents.

5. The compounds of claim 4 wherein V is selected from the group consisting of 3-chlorophenyl, 3-bromophenyl, 3,5-dichlorophenyl, and 2,4-dichlorophenoxy.

6. The compounds of claim 3 wherein V is selected from the group of monocyclic heteroaryl optionally substituted with 1-4 substituents.

7. The compounds of claim 6 wherein V is selected from the group of 2-pyridyl, 3-pyridyl, and 4-pyridyl.

8. The compounds of claim 7 wherein V is 4-pyridyl.

9. The compounds of claim 3 wherein L is phenoxy with 1-2 substituents selected from the group consisting of chloro, fluoro, and nitro.

10. The compounds of claim 9 wherein L is selected from the group consisting of phenyl, $-OC_6H_4NO_2$, $-OC_6H_4Cl$, and $-OC_6H_3Cl_2$.

11. The compounds of claim 10 wherein L is selected from the group consisting of 4-nitrophenoxy, 4-chlorophenoxy, 2,4-dichlorophenoxy, and 3,5-dichlorophenoxy.

12. The compounds of claim 11 wherein L is 4-nitrophenoxy.

13. The compounds of claim 3 wherein L is halogen.

14. The compounds of claim 13 wherein L is selected from the group consisting of Cl and Br.

15. The compounds of claim 3 wherein said compound at C' is the *R*-enantiomer.

16. The compound of claim 15 wherein V is 4-pyridyl and L is 4-nitrophenoxy.

17. The compound of claim 15 wherein V is 4-pyridyl and L is Cl.

18. The compound of claim 15 wherein V is 3-chlorophenyl and L is 4-nitrophenoxy.

19. The compound of claim 15 wherein V is 3-chlorophenyl and L is Cl.

20. The compounds of claim 3 wherein said compound at C' is the *S*-enantiomer.

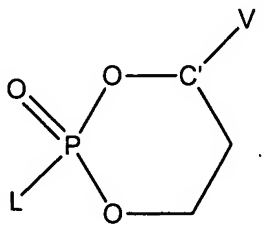
21. The compound of claim 20 wherein V is 4-pyridyl and L is 4-nitrophenoxy.

22. The compound of claim 20 wherein V is 4-pyridyl and L is Cl.

23. The compound of claim 20 wherein V is 3-chlorophenyl and L is 4-nitrophenoxy.

24. The compound of claim 20 wherein V is 3-chlorophenyl and L is Cl.

25. A method for the preparation of compounds of Formula I:



Formula I

wherein V and L are *trans* relative to one another;

V is selected from the group consisting of phenyl and monocyclic heteroaryl, all optionally substituted with 1-4 substituents; and

L is selected from the group consisting of halogen, and aryloxy optionally substituted with 1-2 substituents;

and salts thereof;

comprising steps of:

a. reacting a 1-(V)-1,3-propane diol or salt thereof with L-$P(O)Cl_2$ in the presence of a base;

b. isomerizing the resulting mixture of *trans/cis* isomers with L^- to form the compound of Formula I wherein the ratio of *trans/cis* is about 85/15 or greater; or

c. isolating the *cis* isomer from the resulting mixture; and
treating said *cis* isomer with L^- to form a compound of Formula I wherein the ratio of *trans/cis* is about 85/15 or greater.

26. The method of claim 25 wherein said ratio of *trans/cis* is at least 85/15.

27. The method of claim 25 wherein said ratio of *trans/cis* is greater than 85/15.

28. The method of claim 25 wherein L is selected from the group consisting of phenoxy, $-OC_6H_4NO_2$, $-OC_6H_4Cl$, and $-OC_6H_3Cl_2$.

29. The compound of claim 28 wherein L is selected from the group consisting of 4-nitrophenoxy, 4-chlorophenoxy, 3,5-dichlorophenoxy, and 2,4-dichlorophenoxy.

30. The method of claim 29 wherein L is 4-nitrophenoxy.

31. The method of claim 25 wherein L is a halogen.

32. The method of claim 31 wherein L is selected from the group consisting of Cl and Br.

33. The method of claim 25 wherein said compound at C' is the *R*-enantiomer.

34. The method of claim 33 wherein V is 4-pyridyl and L is 4-nitrophenoxy.

35. The method of claim 33 wherein V is 4-pyridyl and L is chloro.

36. The method of claim 33 wherein V is 3-chlorophenyl and L is 4-nitrophenoxy.

37. The method of claim 33 wherein V is 3-chlorophenyl and L is chloro.

38. The method of claim 25 wherein said compound at C' is the *S* enantiomer.

39. The method of claim 38 wherein V is 4-pyridyl and L is 4-nitrophenoxy.

40. The method of claim 38 wherein V is 4-pyridyl and L is chloro.

41. The method of claim 38 wherein V is 3-chlorophenyl and L is 4-nitrophenyl.

42. The method of claim 38 wherein V is 3-chlorophenyl and L is chloro.

43. The method of claim 25

wherein;
L is selected from the group consisting of aryloxy optionally substituted with 1-2 substituents; and further comprising the use of a solvent system comprising an N-containing heteroaryl solvent.

44. The method of claim 43 wherein said solvent system is used in step a.

45. The method of claim 43 wherein said N-containing heteroaryl solvent is pyridine.

46. The method of claim 25 wherein: in step a. a salt of the 1-(V)-1,3-propane diol is reacted with L-$P(O)Cl_2$ in presence of a base.

47. The method of claim 46 wherein said salt is selected from the group consisting of mineral acid salts.

48. The method of claim 47 wherein said salt is selected from the group consisting of HBr and HCl.

49. The method of claim 48 wherein said salt is HCl salt.

50. The method of claim 25 further comprising isolating the *trans* isomer of compound of Formula I.

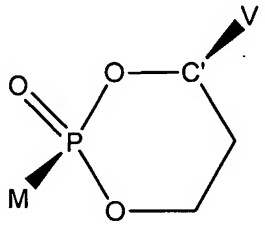
51. The method of claim 50 wherein V is 4-pyridyl and L is 4-nitrophenyl.

52. The method of claim 50 wherein V is 4-pyridyl and L is chloro.

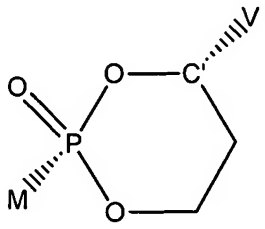
53. The method of claim 50 wherein V is 3-chlorophenyl and L is 4-nitrophenyl.

54. The method of claim 50 wherein V is 3-chlorophenyl and L is Cl.

55. The method of making a compound of Formula II and salts thereof:



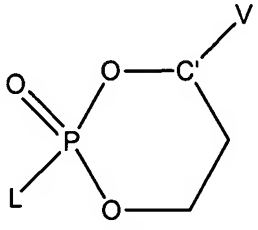
Formula II.A



Formula II.B

comprising:

reacting a compound of Formula I or salts thereof with MH;



Formula I

wherein:

V and L are *trans* relative to one another;

V is selected from the group consisting of heteroaryl, and phenyl, all optionally substituted with 1-4 substituents;

L is selected from the group consisting of halogen, and phenoxy optionally substituted with 1-2 substituents; and

MH is selected from the group consisting of either protected or unprotected oncolytic agents, and antiviral agents and wherein:

H is attached to O, S, or N; and

M is attached to phosphorus via an oxygen, nitrogen or sulfur atom.

56. The method of claim 55 wherein M is attached to phosphorus via an oxygen present in a primary hydroxyl on MH.

57. The method of claim 55 wherein MH is an acyclic nucleoside.

58. The method of claim 55 wherein MH is reacted with a compound of Formula I in the presence of a base.

59. The method of claim 55 wherein MH is a protected nucleoside and further comprising the steps of:

forming an anion of MH with a base; and

adding a phosphorylating agent of Formula I or salt thereof to said anion.

60. The method of claim 55 wherein MH is an unprotected nucleoside, and wherein the compound of Formula I or salt thereof is added to MH or salt thereof.

61. The method of claim 58 wherein said base is R'MgX'

wherein:
R' is selected from the group consisting of C1-C5 alkyl, and aryl optionally substituted with 1-3 substituents;
X' is selected from the group consisting of halogen.

62. The method of claim 61 wherein said base is selected from the group consisting of *tert*-BuMgCl, and phenylMgCl.

63. The method of claim 62 wherein said base is *tert*-BuMgCl.

64. The method of claim 55 further comprising:

forming an anion of a protected nucleoside with a base;
adding a Lewis acid; and
adding a compound of Formula I.

65. The method of claim 55 wherein MH is a nucleoside, and further comprising:

forming an anion of MH with a base;
adding a Mg salt; and
generating the Mg salt of said anion.

66. The method of claim 65 wherein said base is selected from the group consisting of alkali hydride, organometallic base, trialkylamine, and N-containing heteroaryl base.

67. The method of claim 65 wherein:

said base is selected from the group consisting of NaH, LiH, LDA, LHMDS, t-BuOK, and BuLi, Et_3N, diisopropylethylamine, DBU, DABCO, and pyridine.

68. The method of claim 65 wherein said salt is selected from the group consisting of $MgCl_2$, $MgBr_2$, and MgI_2.

69. The method of claim 65 wherein said base is NaH and said salt is $MgCl_2$.

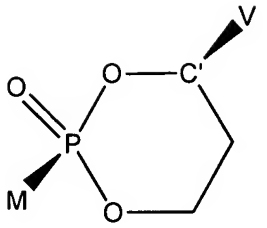
70. The method of claim 65 wherein said base is t-BuOK and said salt is $MgCl_2$.

71. The method of claim 65 wherein said base is BuLi and said salt is $MgCl_2$.

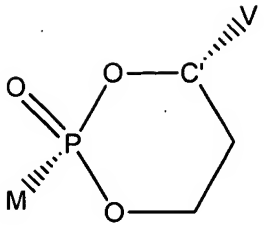
72. The method of claim 65 wherein said base is DBU and said salt is $MgCl_2$.

73. The method of claim 65 wherein said base is Et_3N and said salt is $MgCl_2$.

74. The method of making a compound of Formula II and salts thereof comprising:

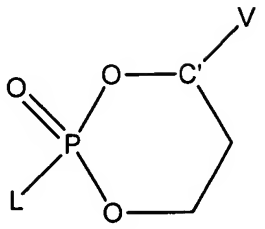


Formula II.A



Formula II.B

reacting a compound of Formula I;



Formula I

wherein:

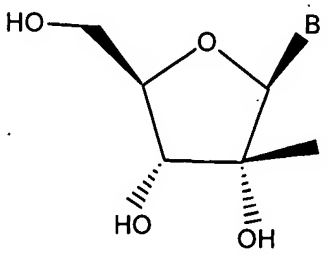
V and L are *trans* relative to one another;

V is selected from the group consisting of heteroaryl, and phenyl, all optionally substituted with 1-4 substituents;

L is selected from the group consisting of halogen, and phenoxy optionally substituted with 1-2 substituents;

and salts thereof;

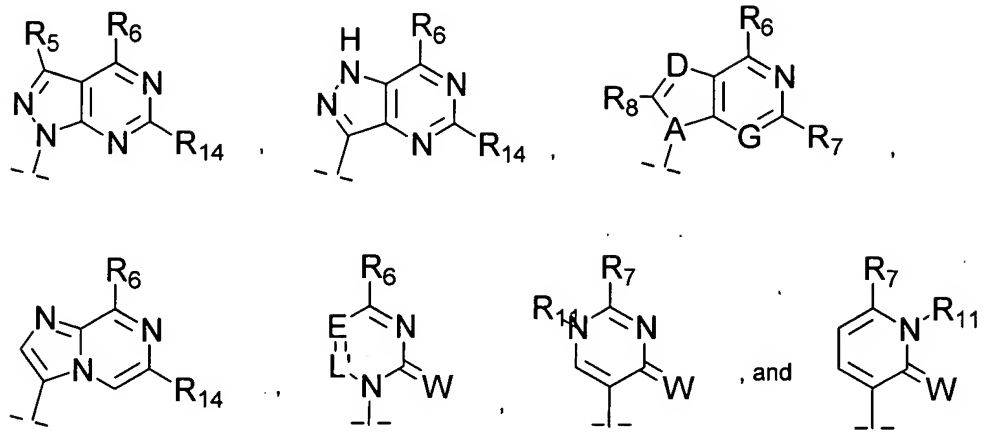
with a nucleoside of Formula III;



Formula III

wherein:

B is selected from the group consisting of



wherein:

A, G, and L' are each independently CH or N;

D is N, CH, C-CN, C-NO_2, C-C_{1-3} alkyl, C-$NHCONH_2$, C-$CONR^{11}R^{11}$, C-$CSNR^{11}R^{11}$, C-$COOR^{11}$, C-$C(=NH)NH_2$, C-hydroxy, C-C_{1-3} alkoxy, C-amino, C-C_{1-4} alkylamino, C-di(C_{1-4} alkyl)amino, C-halogen, C-(1,3oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy;

E is N or CR^5;

W is O or S;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3, or halogen;

R^6 is H, OH, SH, NH_2, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3;

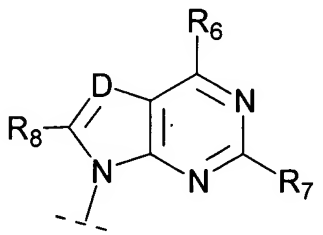
R^7 is H, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, or di(C_{1-4} alkyl)amino;

R^8 is H, halogen, CN, carboxy, C_{1-4} alkyloxycarbonyl, N_3, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, or (C_{1-4} alkyl)$_{0-2}$ aminomethyl;

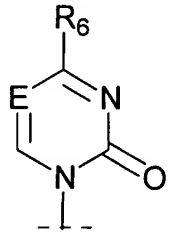
R^{11} is H or C_{1-6} alkyl;

R^{14} is H, CF_3, C_{1-4} alkyl, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, or di(C_{1-4} alkyl)amino.

75. The method of claim 74 wherein B is selected from the group consisting of



, and



;

wherein:

D is N, CH, C-CN, C-NO_2, C-C_{1-3} alkyl, C-$NHCONH_2$, C-$CONR^{11}R^{11}$, C-$COOR^{11}$, C-hydroxy, C-C_{1-3} alkoxy, C-amino, C-C_{1-4} alkylamino, C-di(C_{1-4} alkyl)amino, or C-halogen;

E is N or CR^5;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3, or halogen;

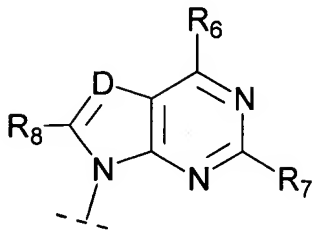
R^6 is H, OH, SH, NH_2, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3;

R^7 is H, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, or di(C_{1-4} alkyl)amino;

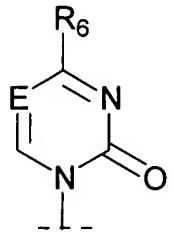
R^8 is H, halogen, CN, carboxy, C_{1-4} alkyloxycarbonyl, N_3, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, or (C_{1-4} alkyl)$_{0-2}$ aminomethyl;

R^{11} is H or C_{1-6} alkyl.

76. The method of claim 74 wherein B is selected from the group consisting of



, and



;

wherein:

D is N, CH, or C-halogen

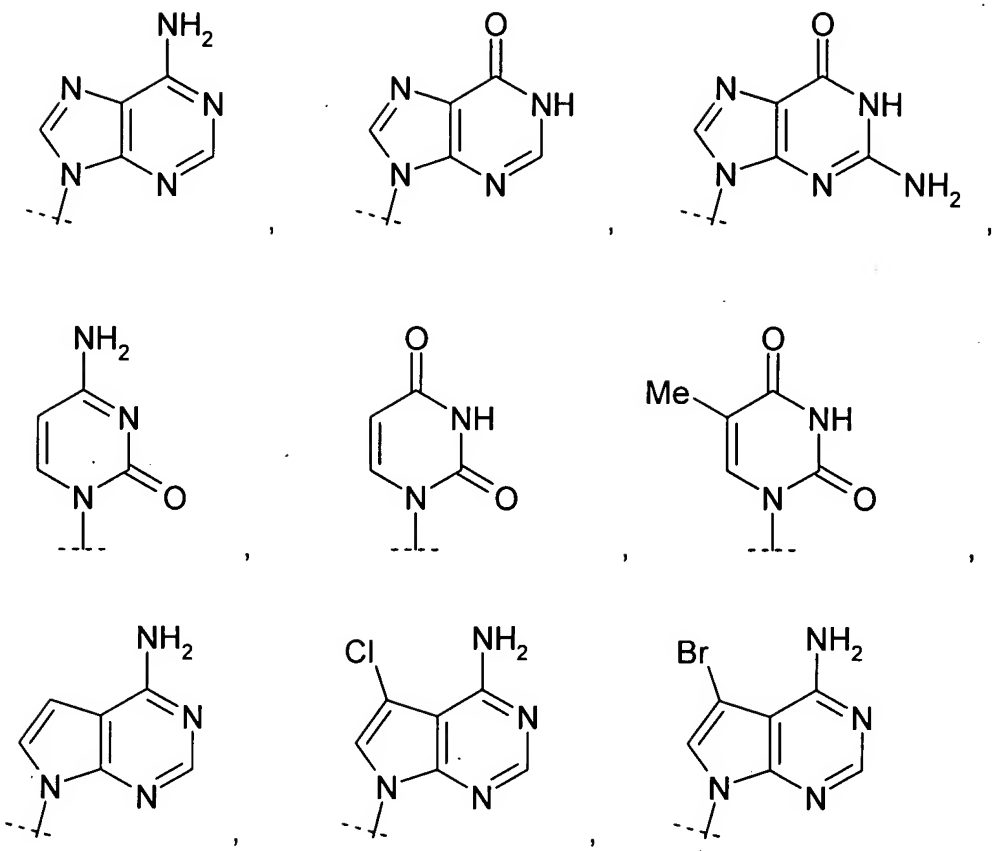
E is N or C-Me;

R^6 is OH, or NH_2;

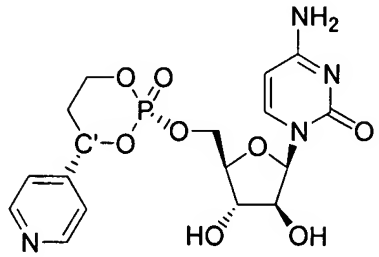
R^7 is H or amino;

R^8 is H or halogen.

77. The method of claim 74 wherein B is selected from the group consisting of

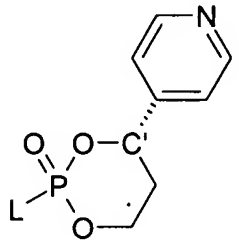


78. A method for the preparation of compounds of Formula V:



Formula V

which comprises coupling a phosphorylating reagent of Formula IV and optionally protected cytarabine;



Formula IV

wherein L is selected from the group consisting of chloro, and 4-nitrophenoxy.

79. The method of claim 78 wherein a base is used in the coupling reaction.

80. The method of claim 79 wherein said base is RMgX wherein:

R is selected from group consisting of C1-C5 alkyl;
X is selected from group consisting of halogen.

81. The method of claim 80 wherein said base is *t*-BuMgCl.

82. The method of claim 78 wherein the hydroxyl groups and 4-amino group of cytarabine are protected.

83. The method of claim 78 wherein the 4-amino of cytarabine is protected as a dimethylformamidine.

84. The method of claim 78 wherein a protecting group for the 2' and 3' hydroxyl groups of cytarabine is selected from group consisting of trialkylsilyl ether, optionally substituted MOM ether, and optionally substituted MEM ether.

85. The method of claim 84 wherein said protecting group for 2' and 3' hydroxyl groups of cytarabine is *t*-butyldimethylsilyl ether.

86. The method of claim 78 wherein the hydroxyl groups and 4-amino group of cytarabine are not protected.

87. The method of claim 86 wherein the L is chloro.

88. The method of claim 78 further comprising:

forming an anion of said optionally protected cytarabine with a base;
adding a Mg salt; and
generating the Mg salt of the anion of said optionally protected cytarabine.

89. The method of claim 88 wherein said base is selected from the group consisting of alkali hydride, organometallic base, trialkylamine, and N-containing heteroaryl base.

90. The method of claim 88 wherein said salt is selected from the group consisting of $MgCl_2$, $MgBr_2$, and MgI_2.

91. The method of claim 88 wherein said base is NaH and said salt is $MgCl_2$.

92. The method of claim 88 wherein said base is t-BuOK and said salt is $MgCl_2$.

93. The method of claim 88 wherein said base is BuLi and said salt is $MgCl_2$.

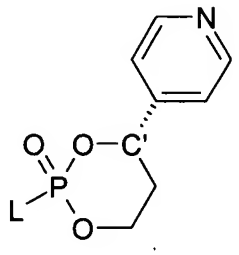
94. The method of claim 88 wherein said base is DBU and said salt is $MgCl_2$.

95. The method of claim 88 wherein said base is Et_3N and said salt is $MgCl_2$.

96. The method of claim 78 further comprising:

using t-BuMgCl as a base;

using a compound of Formula IV



Formula IV

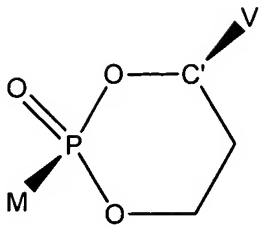
wherein:

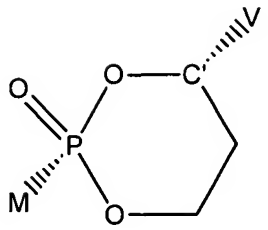
L is 4-nitrophenoxy;

said optionally protected cytarabine has the 2' and 3' hydroxyl groups protected as *t*-butyldimethylsilyl ethers; and

has the 4 amino group protected as dimethylformamidine.

97. The method of making a compound of Formula II and salts thereof:

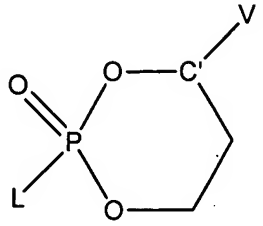




Formula II.A Formula II.B

comprising:

reacting a compound of Formula I or salts thereof with MH;



Formula I

wherein:

V is selected from the group consisting of heteroaryl, and phenyl, all optionally substituted with 1-4 substituents;

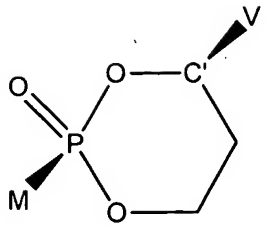
L is selected from the group consisting of halogen, and phenoxy optionally substituted with 1-2 substituents; and

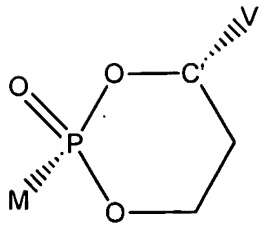
MH is selected from the group consisting of either protected or unprotected oncolytic agents, and antiviral agents and wherein:

H is attached to O, S, or N; and

M is attached to phosphorus via an oxygen, nitrogen or sulfur atom.

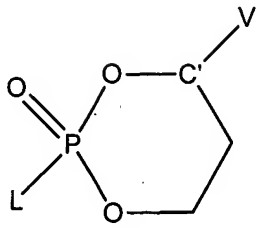
98. The method of making a compound of Formula II and salts thereof comprising:





Formula II.A Formula II.B

reacting a compound of Formula I;



Formula I

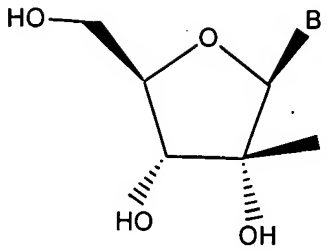
wherein:

V is selected from the group consisting of heteroaryl, and phenyl, all optionally substituted with 1-4 substituents;

L is selected from the group consisting of halogen, and phenoxy optionally substituted with 1-2 substituents;

and salts thereof;

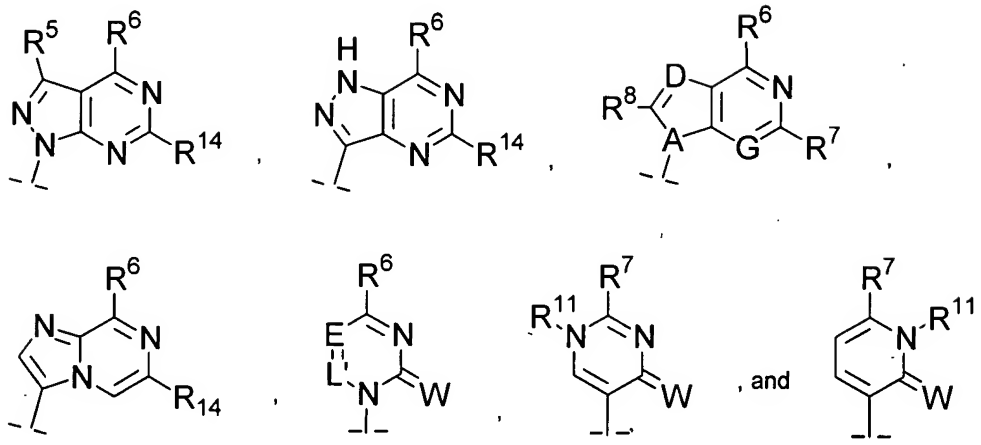
with a nucleoside of Formula III;



Formula III

wherein:

B is selected from the group consisting of



wherein:

A, G, and L' are each independently CH or N;

D is N, CH, C-CN, C-NO_2, C-C_{1-3} alkyl, C-$NHCONH_2$, C-$CONR^{11}R^{11}$, C-$CSNR^{11}R^{11}$, C-$COOR^{11}$, C-C(=NH)NH_2, C-hydroxy, C-C1-3 alkoxy, C-amino, C-C_{1-4} alkylamino, C-di(C_{1-4} alkyl)amino, C-halogen, C-(1,3oxazol-2-yl), C-(1,3-thiazol-2-yl), or

C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy;

E is N or CR^5;

W is O or S;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3, or halogen;

R^6 is H, OH, SH, NH_2, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3;

R^7 is H, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, or di(C_{1-4} alkyl)amino;

R^8 is H, halogen, CN, carboxy, C_{1-4} alkyloxycarbonyl, N_3, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, or (C_{1-4} alkyl)$_{0-2}$ aminomethyl;

R^{11} is H or C_{1-6} alkyl;

R^{14} is H, CF_3, C_{1-4} alkyl, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, or di(C_{1-4} alkyl)amino.